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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,633	01/19/2005	David Grenville Holmes	PC/4-32514A	4568

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
LEWIS, AMY A	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,633	HOLMES ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-16 and 18-26* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-9, 11-13, 18-20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/08, 10/3/06, 5/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II (claims 1, 5-26) and the species formula IC and atherosclerosis as the condition associated with hyperlipidemia, in the reply filed on 8/1/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

Claims 3-5, 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim.

Claims 1 and 6-9, 11-13, 18-20-26 are examined as far as they read upon the elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 6-9, 11-13, 18-20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6166063 (to Villhauer) in view of U.S. Patent No. 6262118 to (Luskey et al.).

Villhauer teaches the instantly claimed compound of formula IC and pharmaceutical compositions thereof (see: abstract; col. 1, lines 30-40); col. 2 lines 18-47). The reference teaches that these compounds are dipeptidyl peptidase-IV (DPP-IV) inhibitors useful in the treatment of conditions mediated by DPP-IV, including non-insulin-dependent diabetes, arthritis, obesity, osteoporosis, and other conditions related to impaired glucose tolerance (see: abstract). Villhauer does not teach treatment of atherosclerosis.

Luskey et al. teaches that diabetes and atherosclerosis are co-morbid diseases (col. 2., lines 1-30):

> Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease… Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density: chylomicrons; very low-density lipoproteins (VLDL); intermediate density lipoproteins (IDL); low density lipoproteins (LDL); and high density lipoproteins (HDL). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states,

> drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

The reference also teaches combination therapy with the following agents for modulating and treating the symptoms and complications of associated atherosclerosis (col. 17, lines 25-60):

> an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as .beta.-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B.sub.6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B.sub.12 (also known as cyanocobalamin); vitamin B.sub.3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the compound of formula IC would be useful to treat hyperlipidemia and atherosclerosis (as an associated condition) because it was known that the compound of formula IC is useful in treating type II diabetes, which is known to be a condition comorbid with hyperlipidemia and atherosclerosis. Therefore, by treating the type II diabetes, one is concomitantly treating the hyperlipidemia and atherosclerosis.

Further, it would have been obvious to administer a combination treatment with other antihyperlipidemic agents, having been taught that it is well known to use such agents in combination therapy for treating hyperlipidemia and atherosclerosis, as taught by Luskey et al. Additionally, MPEP § 2144.06 states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2) Claims 1, 6-9, 11-13, 18-20-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6 and 9 of copending Application No. 11/815536. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to treating hyperlipidemia, and associated disorders such as atherosclerosis) with cyano-pyrolidine DPP-IV inhibitors (see the specification p. 5 of the copending application which discloses the same compound as formula IC).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3) Claims 1, 6-9, 11-13, 18-20-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 11/868129, in view of Luskey et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to treating conditions of impaired glucose tolerance, such as hyperlipidemia, with cyano-pyrolidine DPP-IV inhibitors (see the specification p. 5 of the copending application which discloses the same compound as formula IC).

Luskey et al. teaches that diabetes and atherosclerosis are co-morbid diseases (col. 2., lines 1-30):

> Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease… Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density: chylomicrons; very low-density lipoproteins (VLDL); intermediate density lipoproteins (IDL);

> low density lipoproteins (LDL); and high density lipoproteins (HDL). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the compound of formula IC would be useful to treat hyperlipidemia and atherosclerosis (as an associated condition) because it was known that the compound of formula IC is useful in treating type II diabetes, which is known to be a condition comorbid with hyperlipidemia and atherosclerosis. Therefore, by treating the type II diabetes, one is concomitantly treating the hyperlipidemia and atherosclerosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4) Claims 1, 6-9, 11-13, 18-20-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8 of copending Application No. 11/497130 in view of Luskey et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to treating hyperlipidemia, i.e., disorders which may be treated by inhibiting HMG-CoA reductase with cyano-pyrolidine DPP-IV inhibitors (see the specification p. 5 of the copending application which discloses the same compound as formula IC).

Luskey et al. teaches combination therapy with the following agents for modulating and treating the symptoms and complications of associated atherosclerosis (col. 17, lines 25-60):

> an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as .beta.-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B.sub.6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B.sub.12 (also known as cyanocobalamin); vitamin B.sub.3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the compound of formula IC would be useful to treat hyperlipidemia and atherosclerosis (as an associated condition), especially in combination therapy, having been taught by Luskey et al. that the compound of formula IC, alone and in combination therapy, is useful in treating hyperlipidemia and atherosclerosis. Further, it would have been obvious to administer a combination treatment with other antihyperlipidemic agents, having been taught that it is well known to use such agents in combination therapy for treating hyperlipidemia and atherosclerosis, as taught by Luskey et al. Additionally, MPEP § 2144.06 states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually

taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) Claims 1, 6-9, 11-13, 18-20-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of hyperlipidemia and associated atherosclerosis, does not reasonably provide enablement for *prevention* hyperlipidemia and associated atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of such experiments are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The nature of the invention & breadth of the claims:

The claims are directed to the treatment and prevention of hyperlipidemia and associated atherosclerosis with the compound of formula IC.

The relative skill of those in the art:

The relative skill of those in the art is high, generally that of an M.D. and or M.D./Ph.D.

The presence or absence of working examples:

Applicants allege the effect of compound IC in lowering triglyceride, total cholesterol, LDL, and VLDL levels in humans compared to placebo, but do not provide any data to this effect. See specification Example 1 at pages 21-22.

The state of the prior art & the predictability/unpredictability of the art:

The state of the prior art regarding the treatment of hyperlipidemia, atherosclerosis and associated diseases is complex as well as unpredictable. As is demonstrated by the Kanter et al. (Circulation Research 2007; 100: 796-781), there are a wide variety of factors, especially when combined with the complexity of the comorbid disorders that occur along with hyperlipidemia and atherosclerosis, involved in the pathology of hyperlipidemia and atherosclerosis. The Kantor article lists hyperglycemia accelerated lesion initiation, VCAM-1 levels, proteoglycan levels,

matrix metalloproteinase regulation, and genetic factor as just some of the factors involved in atherosclerosis lesion formation.

The NCEP Report (Grundy et al., Implications of Recent Clinical trial for the Nat'l Cholesterol Education Program..., *Arterioscler Thromb Vasc Biol.* 2004 Aug;24(8):e149-61), discussing results of clinical trials regarding hyperlipidemia (cholesterol, trigyyceride levels, incidence of coronary artery disease, etc.), is evidence that hyperlipidemia and atherosclerosis prevention is complex and has yet to be attained through a single pharmacological regimen.

For inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, as is the case for preventing hyperlipidemia and atherosclerosis, more evidence is required to show possession (MPEP § 2163).

The specification does not enable a person skilled in the art to which is pertains to make or use the invention commensurate in scope with the claims. Applicants have failed to provide guidance and information sufficient to allow the skilled artisan to ascertain that the present active agents are effective against prevention of hyperlipidemia and associated atherosclerosis. The limited enablement for treatment of hyperlipidemia is noted but does not support a conclusion that all prevention can be attained with the claimed active agents. Such prevention of hyperlipidemia and atherosclerosis cannot be accomplished with any reasonable certainty or without undue burden of experimentation.

Absent a reasonable *a priori* expectation of success for using compounds of formula IC to prevent hyperlipidemia and atherosclerosis, the practice of the invention, as it is claimed in its

current scope, would require an undue amount of experimentation because the specification provides inadequate guidance to do otherwise.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is 571-272-9032. The examiner can normally be reached on Monday-Friday 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy A Lewis/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614